The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte ANDREW S. JANOFF, THOMAS D. MADDEN,
PIETER R. CULLIS, JOHN J. KEARNS,
and ANTHONY G. DURNING

_____

Appeal No. 2001-1245
Application 08/430,661

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH, and POTEATE, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 77-81, 83-85, 89, 91 and 92, all the claims remaining in the application. Claim 77 is representative of the subject matter on appeal and reads as follows:

77. A method of preparing a drug-lipid complex comprising the steps of:
(a) dissolving a lipid which comprises a fatty acid or a phospholipid in an organic solvent selected from the group consisting of chloroform, methanol, dimethysulfoxide (DMSO), methylene chloride, cholorform:methanol mixtures and benzene:methanol mixtures;
(b) dissolving a polyene antifungal agent in an organic solvent;

(c) combining the product of step (a) and the product of step (b) so as to obtain a mixture of the lipid solution and the agent solution;
(d) adding an aqueous phase to the product of step (c); and
(e) removing organic solvent from the mixture of step (d),
wherein the complex has no captured volume, wherein the complex is substantially free of liposomes and wherein the relative amount of polyene antifungal agent used is such that the agent comprises from about 25 to 50 mole percent of the complex.

The references relied upon by the examiner are:

Fukushima et al. (Fukushima)	4,687,762	Aug. 18, 1987
Moro et al. (Moro)	GB 2041871A	Sep. 17, 1980
Heyne[1]	EP 0,069,307	Jan. 12, 1983

Claims 77 through 81, 83 through 85, 89, 91 and 92 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon Fukushima by itself or Fukushima and Moro or Fukushima and Heyne. We reverse.

BACKGROUND

As seen from claim 77, the claimed invention is directed to a method of preparing a drug-lipid complex which comprises a series of five steps. The complex contains a polyene antifungal agent and a lipid which comprises a fatty acid or a phospholipid. As explained in the last clause of claim 77, the complex has no captured volume, is substantially free of liposomes and the relative amount of polyene antifungal agent used in the method is such that the agent comprises from about 25 to 50 mole percent of the complex.

[1] The record copy of this document is in the German language. For reasons unclear from the record, the examiner did not request a translation of the document and was satisfied to consider its disclosure on the basis of the English language abstract attached thereto. Appellants attached a translation of the underlying European Patent Application to the Reply Brief. Our consideration of the issues on appeal has been based upon the full text translation supplied by appellants to whom we express our appreciation.

In considering the issues in this appeal, one must be careful to distinguish between the claimed drug lipid complex and liposomes since the method required by claim 77 prepares the complex in such a manner that the composition is "substantially free of liposomes." Appellants make clear that the drug-lipid complex of claim 77 can be made by "techniques substantially the same as those for making liposomes." Specification, page 1.

The specification sets forth various methods for preparing the drug-lipid complex of the present invention. For example, appellants explain at page 7 of the specification:

> Various methods for preparing the HDLCs [high drug:lipid complexes] of the invention are disclosed; for example, techniques that first solubilize the drug, specifically amphotericin B in a solvent such as DMSO or methanol. The lipid (preferably DMPC:DMPG in a 7:3 mole ratio) is solubilized in a solvent such as methylene chloride, and the lipid and dug solutions mixed. The solvents may be evaporated under reduced pressure, resulting in a thin lipid-drug film. The film may be hydrated in an aqueous solution such as saline, PBS, or glycine buffer, forming HDLCs. Alternatively, the aqueous solution may be added to the solvent-containing drug and lipid phase prior to evaporation of the solvent. As another alternative, the resulting dry lipid-drug film may be resuspended in a solvent, such as methylene chloride and again evaporated under reduced pressure prior to hydrating the film. A dehydration procedure may also be used; in this process a dry lipid-drug film is dehydrated to form a flake which is hydrated with aqueous solution.

In performing the method described in the specification with an eye to making compositions which are drug-lipid complexes free of liposomes as opposed to making compositions which are substantially liposomal with some drug-lipid complex, one must pay attention to amount of the drug used. Appellants explain "preparations employing 25 mole percent to about 50 mole percent of drug are substantially HDLCs, free of liposomes. Alternatively, preparations containing 5 mole percent hydrophobic drug and less are substantially liposomal with some HDLCs." Specification, page 6.

DISCUSSION

The statement of the rejection appears on page 3 of the Examiner's Answer and due to its brevity we reproduce it as follows:

> Fukushima teaches lipid-drug complexes and a method of preparation of the complexes. The method differs from the instant method in that the solvent is evaporated after the addition of the aqueous medium. This step is deemed to be a manipulatable parameter by an artisan since it is well known in the art that the solvent can be removed before or after the addition of the aqueous medium as is also evidenced from the references of GB [Moro] and HOFF [Heyne] (note the abstracts). An artisan would be motivated to manipulate the basic steps taught by Fukushima to obtain the best possible results based on the knowledge in the art as shown by GB [Moro] or HOFF [Heyne]

In reviewing the issues presented in this appeal, there are three requirements of claim 77 which are key in deciding the appeal, (1) adding an aqueous phase to the product of step (c), (2) the complex comprising a polyene antifungal agent and (3) the polyene antifungal agent comprised from about 25 to 50 mole percent of the complex. As can be seen from the examiner's statement of rejection, only the sequence of steps is addressed. The examiner has made no finding in the statement of the rejection in regard to the polyene antifungal agent being used as the active agent or that the polyene antifungal agent being used in the amount required by claim 77. Thus, the examiner's statement of the rejection is incomplete, and as a result is difficult to review.

Also hindering review of the examiner's position on appeal is that the statement of the rejection only states what one of ordinary skill in the art would have purportedly been "motivated" to do and does not set forth what one of ordinary skill in the art would have found obvious. The latter is the statutory standard of 35 U.S.C. § 103(a) while the former is but one factor to take into account in reaching a conclusion as to whether the subject matter of a given claim as a whole would have been obvious.

Be that as it may, our review of the examiner's position leads us to conclude that the examiner has not established a prima facie case of obviousness. Turning first to the rejection as it stands premised upon Fukushima by itself, as noted, the examiner has made no findings in regard to the requirement of claim 77 that the complex contain a polyene antifungal agent. We do note that the examiner, in responding to appellant's arguments on appeal, states at page 5 of the Examiner's Answer that "Fukushima is directed to water insoluble drugs in general… and it is within the skill of the art to make use of the method to any drug." We remind the examiner that conclusions of obviousness must be based upon facts, not generalities. In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968); In re Freed, 425 F.2d 785, 788, 165 USPQ 570, 571 (CCPA 1970). The examiner has not provided an analysis of the relevant disclosure of Fukushima as to the class of drugs useful in that invention and correlated that description to the properties of the polyene antifungal agent required by claim 77 on appeal. Without such a reasoned analysis, we are not in a position to determine whether polyene antifungal agents as required by claim 77 on appeal are indeed within the class of drugs envisioned by Fukushima. Furthermore, even if such an analysis establishes that the polyene antifungal agents of this invention are within the broad definitions of "drugs" included in Fukushima, that does not necessarily mean it would have been obvious to one of ordinary skill in the art to select that subgenus of agents from the broad genus of "drugs" described by Fukushima. See In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941(Fed. Cir.1992).

Nor has the examiner taken into account the requirement of the claims that the polyene antifungal agent must comprise from about 25 to 50 mole percent of the complex. We note that Fukushima does provide some information in regard to the percent incorporation of the drug in the complex in that invention. See, e.g., Table 1. However, those data are based upon drug/phospholipid w/w %. The examiner has not presented a reasoned analysis why the percent drug incorporation described in Fukushima would necessarily teach or suggest the requirement of claim 77 on appeal that the polyene antifungal agent comprise from about 25 to 50 mole percent of the complex.

The examiner's consideration of the issue of the sequence of steps required by claim 77 vis-à-vis the sequence of steps described in Fukushima is equally lacking. The examiner agrees that Fukushima prepares the drug/lipid complex of that invention using a sequence of steps in which a solvent solution of a water-insoluble drug and a phospholipid is first treated to remove the solvent by evaporation to leave behind a drug-containing phospholipid film. It is after the solvent is removed that an aqueous phase is introduced in the process. This is the exact opposite of what is required by claim 77 on appeal in that the aqueous phase according to the claimed method is added to product at step (c) which comprises a solvent solution of the lipid and polyene antifungal agent. As seen from the statement of rejection, the examiner has "deemed" the step to be a " manipulatable parameter." The examiner then asserts that "it is well known in the art that the solvent can be removed before or after the addition of the aqueous medium."

We again remind the examiner that obviousness must be based upon facts not generalities. The examiner has not explained what facts appear in Fukushima or knowledge generally known to one of ordinary skill in the art which would reasonably lead one to conclude that the sequence of steps described in Fukushima may be altered to arrive at the subject matter of claim 77 on appeal.

For these reasons, the examiner's rejection as based on Fukushima alone is reversed.

Considering Fukushima in light of Moro or Heyne does not aid the examiner's case. From the statement of the rejection, we believe the examiner is under the impression that Moro and Heyne describe the sequence of steps required by the claim 77 on appeal. If that is the examiner's position, we do not find that it is supported by either reference. First, Moro and Heyne are directed to forming liposomes, not drug-lipid complexes as required by claim 77 on appeal. Thus, the relevance of these references in considering the obviousness of the subject matter of claim 77 is subject to question.

Turning to Moro, we find that it describes a method for forming liposomes in which an aqueous solution of the drug is added to a solvent solution of the lipidic component. See, e.g., page 1, lines 86-95. Claim 77 requires preparation of separate solvent solutions of the lipid and polyene antifungal agent which are subsequently combined. Thus, even apart from being directed to a method for forming liposomes, the method described by Moro is further removed from what is required by claim 77 and in our view presents no reason, suggestion or motivation to modify the procedure specified in Fukushima in the manner required by claim 77 on appeal.

Heyne describes a procedure similar to that of Moro. As seen from page 4 of the translation, the active agents are added to the solution of substances which will form the liposome, apparently either directly in the case of lipophilic active substances or as an aqueous solution in the case of hydrophilic active substances. Suffice it to say the examiner has not established that Heyne describes the sequence of steps required by claim 77 on appeal or provided sufficient reasons why one of ordinary skill in the art would have found it obvious to alter the sequence of steps described in Fukushima in order to arrive at the subject matter of claim 77.

The examiner's rejection as it is based on the combination of Fukushima and Moro or Fukushima and Heyne is reversed.

The decision of the examiner is reversed.

REVERSED

Sherman D. Winters
Administrative Patent Judge

William F. Smith
Administrative Patent Judge

Linda R. Poteate
Administrative Patent Judge

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